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# REPORT ON

# VACCINATION-RELATED RESEARCH PROJECTS

# AND

# RECOMMENDATIONS REGARDING FUTURE PROJECTS

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## INTRODUCTION

Financial support for vaccination-related projects is justified for a number of reasons, but primarily because of the enormous human and economic benefits that result from funds spent on disease prevention by immunization - probably the greatest return for any health-care dollar. IDRC should play a part in such financing because there are vaccine-related needs that would probably not otherwise be met by other granting agencies, which often concentrate their attention on vaccine development and large scale trials of immune responses and efficacy. While these are vital aspects, various local circumstances may necessitate some modification of generally accepted vaccination policies or procedures, and investigation of such instances may be very important to optimize the effectiveness of vaccination policies in a particular country or region.

In this report, an assessment has been made of the various categories of project that have been funded for vaccination-related topics since 1980, and also of applications currently under consideration. A proposed strategy for the Centre in dealing with future activities in this field has been drawn up, and an outline of a recommended policy is given.

VACCINATION-RELATED PROJECTS SUPPORTED 1980 TO DATE

For purposes of comment, these have been classified into six categories.

1. Data collection pertinent to the development or modification of vaccination policy in the recipient country

The vaccines (and countries) were:

Hepatitis B (Malaysia, Philippines, St. Kitts, Mozambique, China)

Polio and DPT (Jamaica, Thailand)
Rubella (Malaysia)
Japanese encephalitis (Thailand)
Measles (Philippines)

Comment - Vaccination policies have to be devised for developing countries because policies formulated for North America and Europe are often inappropriate since there are many differences in disease incidence, health care delivery systems, socio-economic factors etc. To devise an appropriate policy, data must be collected and analyzed to enable the optimal dosage to be given at practicable and appropriate time intervals. Studies such as those listed above provide such assistance to the authorities of the countries concerned and should continue to be supported with high priority.

It may be appropriate for apparently similar studies to be undertaken in more than one country. Local conditions can affect immune responses. For example, in some countries certain enteroviruses may commonly circulate in a country and cause widespread symptomless infection of the intestinal tract. Such infected persons may not respond to a dose of oral polio-vaccine (OPV) and as few as half the recipients of an OPV course may be rendered immune. Whereas in another country where such endemic viruses are uncommon, more than 90% of recipients may become immune after a course. Where it is known or believed that local circumstances may affect the response to vaccines, studies are well worth support.

2. Evaluation of the effectiveness of vaccines and vaccine programmes

BCG (Korea, Haiti, Kenya)
DPT and Polio (Thailand) - a vaccine trial centre.

Comment - Assessment of the effectiveness of BCG has been the subject of some major research projects, eg. India. Results have been controversial. It is not a suitable subject for small scale studies, and is not recommended for IDRC support. Research on TB incidence is useful but trends should not be ascribed to BCG exclusively since many other factors play a role.

The support for a vaccine Centre in Thailand is commended.

3. Study of factors which may influence the immune response to vaccines

Nutritional state - (Senegal, Colombia) (BCG, measles, tetanus)
Schistosomiasis - (Egypt) (Hepatitis B)

Comment - These factors may interfere with development of immunity and necessitate adjustment of dosage and schedules to achieve the best response. This may be of great importance in some countries and regions, and research locally into the effects and ways to rectify them should be supported.

4. Support for vaccine production and development

Yellow fever (Brazil, Colombia, Nigeria)

Comment - Improvements in vaccine production facilities were supported. This is not research and might be more properly funded by CIDA. A component in Brazil, however, on developing a cell culture methodology for vaccine production, was appropriate for support.

5. Maintenance of vaccine potency

Measles (PATH, USA)

Comment - Evaluation of a new time-temperature visual indicator of improper handling procedures for vaccine was a useful exercise and worth funding. Deterioration of vaccines during storage or transport is a major problem in developing countries and a simple indicator certainly deserved field evaluation.

6. Non-microbial vaccine research

Anti-pregnancy (India, Chile)

Comment - I have no expertise in this subject but it appears to be exciting and of great potential, though it is a lengthy and expensive project. It is progressing.

PIPELINE PROJECTS

These are categorized numerically as in the previous section.

1. Data collection pertinent to vaccination policy

Hepatitis B (Malaysia/S. Korea/Philippines)
Measles (Cameroon, Sudan)

Comment - The tri-centre hepatitis study has a number of objectives and is a composite of three distinct projects. The portions that deal with the integration of an infant vaccination schedule into the EPI programmes is pertinent and topical, and is relevant to the Centre's objectives. The Korean sub-project, however, includes a clinical trial of dosage schedules and efficacy of two Korean plasma-derived HB vaccines, and such a proposal would not normally be regarded as suitable for IDRC support.

The measles vaccine projects are scientifically sound evaluations of vaccination at 5 or 6 months of age - either with a higher dose or with the more potent Edmonston-Zagreb Virus strain - and are appropriate subjects. A similar project in the Philippines has already been accepted by IDRC. This is a subject of much current interest and other studies may be nearing completion. It may be prudent to make enquiries in this regard before reaching a decision on these two. (see Appendix 1)

2. Evaluation of effectiveness of vaccines

BCG (Zambia, Uganda)

Comment - As indicated in my earlier comments, BCG efficacy studies are not considered appropriate subjects for IDRC support.

3. Study of factors influencing the immune response

Hepatitis B - Schistosomiasis (Egypt)

Comment - This application was prompted by an observation of a decreased antibody response to HB vaccine in infants of mothers infested with S. mansoni. Further study of this problem is necessary since it would pose a major difficulty in designing vaccination schedules for infants in regions with widespread schistosome infesta-

tion. I believe this is a highly appropriate topic for IDRC support.

4. Support for vaccine production and development

Japanese encephalitis (Thailand/Canada)

Comment - This proposal concerns molecular biological research into the possibility of devising a synthetic peptide vaccine and, if successful, the transfer of the technology to Thailand. The initial work will be highly academic research in Canada and the project is **not recommended for IDRC support.**

5. Maintenance of vaccine potency

There are no pipeline projects in this category.

6. Non-microbial vaccine research

Snake-bite vaccine (Thailand)

Comment - While this is outside my areas of experience, the proposal is interesting and seems to be appropriate for financial support from the Centre.

## CONSIDERATIONS RELEVANT TO FUTURE STRATEGY REGARDING VACCINATION-RELATED APPLICATIONS

Applications for financial support expected to be received by IDRC in relation to vaccines and vaccination are likely to include proposals for research into the following aspects:

- -improvements in existing vaccination programmes
- -design of new vaccination policies and programmes
- -evaluation of the impact of vaccination programmes

These three aspects will be briefly reviewed below and from this discussion topics that seem most appropriate to the objectives of IDRC will be chosen in the formulation of a policy for the future.

Proposals that include research projects that are regarded as the responsibility of the developer or manufacturer of a vaccine, such as trials of immunogenicity, safety and efficacy, or major projects such as the establishment of vaccine production facilities in developing countries, are considered inappropriate for IDRC support and are not commented upon.

### A. Improvements in Existing Vaccination Programmes

This covers a broad class of possible proposals. Some of the more relevant aspects have been chosen for comment.

#### 1. Protection of children at an earlier age than at present

Infants should be immunized at the earliest time after birth that vaccine can be given safely and stimulate a reliable protective response. Antibody derived from the mother may interfere with the response to early vaccination with some immunizing agents but improved, more potent products are becoming available that permit effective immunization at earlier ages than hitherto. An example, presently under IDRC-supported trial, is the Edmonston-Zagreb measles vaccine which it is hoped can be effectively administered at 5 months of age rather than at the current 9 months.

The response to early vaccination with some vaccines will be dependent on maternal antibody, as indicated, but the proportion of mothers with antibodies to various organisms varies from one generation to the next, particularly in a country where hygiene and socio-economic conditions have changed in recent decades. Thus early vaccination deserves constant review. The potential to save infant lives is great and applications deserve serious consideration.

2. Studies of the effect on vaccine-induced immunity of rectifiable or treatable conditions

The nutritional state or the presence of an infection or infestation, whether symptomatic or not, may affect the response to vaccination.

Proposals may involve research: (a) to determine the effect of malnutrition or a parasitic infection (e.g. schistosoma) on the immune response or (b) to modify the vaccination schedule, such as by a larger dose or more doses, so as to compensate for the adverse condition if it cannot be rectified or eradicated. Both aspects of research are likely to lead to improved immunity in the population concerned, which may vary from a small community to a large region. It is worthwhile research.

3. Determination of the minimum effective dose of a vaccine

Some recently developed vaccines (e.g. hepatitis B) have been reported to be effective in smaller doses than are generally recommended. It is likely that workers in some developing countries will wish to explore this aspect in their own jurisdiction since it will reduce costs and has the potential for reducing the incidence of adverse reactions. Properly designed studies to study reduced dosage are suitable for support.

4. Comparative studies of improved immunizing preparations

There may be more potent vaccines than those presently in use (e.g. enhanced potency inactivated polio vaccine- IPV; Edmonston-Zagreb measles vaccine) or newly marketed combinations of vaccines (DPT plus enhanced potency IPV). Combination "cocktails" have the virtue of often permitting shortening of a schedule and reduction in the number of mother/child visits.

Another preparation which may be available in a few years is an acellular pertussis vaccine, which is expected to replace the whole cell pertussis vaccine that is a component of DPT. Clinical and efficacy trials of acellular pertussis vaccine and of enhanced potency IPV are expected to be major projects that would be beyond the scope and objectives of IDRC, but applications related to more local issues of their usage in certain countries may be expected and might be appropriate.

B. Design of new vaccination policies and programmes

As new vaccines become available, their role in disease prevention in each country has to be determined. The costs and

benefits need to be evaluated and will vary with the incidence of disease and many other factors. Even when widespread or universal use of a vaccine is considered desirable, matters of scheduling and integration with other vaccination programmes or health care visits remain to be determined. The possible integration of hepatitis B vaccine into the EPI is an example which has already led to a proposal to IDRC. It is a relevant and important matter that requires research for its resolution.

Other new vaccines that lie ahead include oral typhoid vaccine and oral cholera vaccine. When these have been proven safe and effective, their role in developing countries will have to be defined. To whom should they be given and when? Such proposals should be appropriate for support from the Centre since local circumstances will probably be an important consideration in the decisions.

C. Evaluation of the impact of vaccination programmes

Costly major immunization programmes are in effect in many countries. It is important to assess the impact of the programmes on the incidence of diseases that are their targets. Only in this way can deficiencies be detected, their cause determined and remedial measures be taken.

Research projects devised to **develop** effective and practicable **disease surveillance systems and vaccination record systems** are necessary in many countries to ensure that data collected is valid and, when appropriately analyzed, will lead to meaningful conclusions. This monitoring is of great importance in any determination that the funds expended on vaccination are having the desired and optimal effect. Innovative proposals deserve support.

Another means of assessing that vaccine administration is being effectively performed with potent vaccine is the detection of serum antibody following vaccination. Laboratory testing is often unavailable or is much too expensive for this purpose, but a number of simple, rapid, economical and highly specific devices or "kits" are becoming available by which antibody can be detected. If these can be shown by research studies to be suitable for field use, a valuable rapid means of assuring the quality of the immunizing procedure would be available. The specificity is usually determined by a monoclonal antibody component in the kit. **Support for field use of rapid economical antibody detection kits** would be of appropriate.

Improvements in procedures for **assessing the impact of vaccination** programmes, both EPI and non-EPI, **on disease incidence** would be of great value in many countries. Innovative ideas that might meet this objective should be encouraged and supported.

RECOMMENDATIONS FOR A POLICY FOR SUPPORT OF VACCINATION-RELATED PROPOSALS

It is recommended that the Centre provide support for research projects designed to facilitate the optimal use of vaccines in preventing disease in the recipient country.

The unique status and activities of IDRC could best be utilized by giving particular emphasis and priority to aspects that may involve uncommon or unusual local circumstances in a country or region which might require modifications of policies or programmes in general use in developing countries.

The categories of application that deserve support have been divided into two groups: one "recommended for support" and the other "suitable for support". This distinction is made on the likelihood that the granting agencies would receive and approve applications on the topics concerned. Categories of proposal in both groups would provide practical useful information of value in developing countries, but for those in the "suitable for support" group, care should be taken to ensure that there is no superfluous duplication of studies already in progress, as they are of more general scope and less dependent upon local circumstances.

Categories of proposal recommended for support:

1. Strategies on the optimal usage of vaccines in communities, countries or regions in which conditions are known or believed to exist which may diminish the immune response. Such conditions may include severe malnutrition, a high incidence of certain infections or infestations (whether apparent or inapparent) etc.

2. Studies of the most effective use of newly licenced vaccines, such as oral typhoid vaccine and oral cholera vaccines which are expected to become available in the near future. Determination of the target population most likely to benefit from such vaccines in areas of both high and low endemicity would be valuable. (see Appendix 2 )

3. Proposals relating to evaluation of the impact of vaccination programmes. These may include a variety of topics from innovative ideas regarding record-keeping or disease surveillance appropriate for the locality or country to trials of the field use of simple antibody detection kits that would assist in determination of immunity in areas without laboratory support.

Categories of proposal suitable for support

These include subjects that may be expected to be supported by other funding agencies also.

1. Proposals for the immunization of children at an earlier age than is now undertaken.

2. Studies on the optimum usage of combination of vaccines in a single preparation.

3. Determination of the minimum dose of a vaccine that will reliably confer immunity.

4. Comparative studies of newly available and potentially more potent vaccines with existing vaccines.

5. Feasibility and design studies for new vaccination programmes, such as addition of hepatitis B vaccine to the EPI.

Categories of proposal that will generally not be suitable for funding

1. Development or clinical trials of new or improved vaccines.

2. Large-scale efficacy trials of new or existing vaccines.

3. Establishment of or modifications to vaccine-production facilities.

4. Studies that would merely confirm existing knowledge of vaccines or vaccine programmes.

# APPENDICES

## APPENDIX 1 Trials of Edmonston-Zagreb Measles Vaccine

A number of studies of the serological response to the Edmonston-Zagreb strain of measles vaccine in infants less than 9 months of age are being undertaken in developing countries. The following list is of those which staff at the Centers for Disease Control, Atlanta, believe will be completed by July 1989 (except Haiti - probably October 1989; and Gambia and Peru, date uncertain). An indication of the supporting or sponsoring agency or institution is given.

| | |
|---|---|
| Mexico - | USAID; CDC and Ministry of Health |
| Senegal - | Task Force on Child Survival |
| Gambia - | Medical Research Council, U.K. |
| Tanzania - | R.I.T. |
| Haiti - | Johns Hopkins University |
| Zanzibar - | Save the Children Fund; R.I.T. |
| Peru - | Johns Hopkins University |
| Togo - | (unavailable) |

The list is not comprehensive, but is illustrative of the multiplicity of studies currently being completed.

## APPENDIX 2 Newly Developed Oral Vaccines for Enteric Diseases

Licensure is likely within the next few years of new typhoid and cholera vaccines which are administered orally. For example, the Ty21a typhoid vaccine has been tested with encouraging results in Egypt and is now being studied in Chile, a country of high endemicity. In Chile, the most appropriate usage may be mass vaccination of school-children (Ferreccio *et al*. J. Infect. Dis., 1989, 159, 766), whereas in countries with different epidemiological patterns a quite different approach may be better. Likewise, the optimal dosage in areas with different degrees of endemicity has yet to be determined. Furthermore, the value of a combined cholera-typhoid oral vaccine remains to be established. Many of these aspects may, in the future, be appropriate subjects for IDRC support, as national authorities seek data on which to decide the most effective use of these new agents in their own jurisdictions.